Applying Maternal Serum and Amniotic Fluid CRP Concentrations, and Cervical Length to Predict Preterm Delivery

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Abstract

Objective: To investigate the clinical advantage of several prognostic factors for predicting preterm delivery.

Materials and methods: Eighty and six patients with a singleton pregnancy admitted to Vali-Asr hospital underwent genetic amniocentesis between the 15th and 23th weeks were included in this study. Maternal serum C-reactive protein (CRP), transvaginal sonographic measurement of cervical length (CL),were examined on genetic amniocentesis time. Receiver-operating characteristic (ROC) analysis was performed to determine the efficacy of maternal serum and amniotic fluid CRP levels in predicting women with preterm delivery. Correlation between each factor and the duration of pregnancy was investigated.

Results: The prevalence of spontaneous preterm delivery before 37 weeks of gestation was 11%. ROC analysis revealed that maternal serum CRP level was the parameter, which had a significant power in the prediction of preterm delivery. The optimum cut-off level was 1.2 mg/L. The sensitivity and specificity were 95.1% and 91.8%, respectively. The positive predictive value for CL length with the cut off value of 25 mm was 72.1%. No statistically significant difference correlation observed between CL and the duration of pregnancy or amniotic fluid and maternal serum CRP levels.

Conclusion: The maternal serum CRP level has a good sensitivity and specificity in the prediction of preterm delivery and this may be helpful in predicting preterm delivery during genetic amniocentesis. Maternal serum CRP measurement is a safe, simple clinically useful, cost effective, non invasive method, that may assist clinicians in evaluation for high-risk patients and determine strategies for the prevention of preterm delivery.

Keywords: Cervical Length, C-Reactive Protein, Preterm Delivery, Amniotic Fluid

Introduction

Preterm delivery (PTD) is a main problem in obstetrics, this cause 70% of perinatal mortality and almost 50% of long-term neurological morbidity (1). Preterm birth is the most cause of perinatal mortality and morbidity (2). But advances in perinatal care, the incidence of preterm birth continues up primarily due to increased multiple pregnancies as a result of assisted reproduction (3). Increase risk of preterm birth is associated with many factors, such as

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socioeconomic marginalization, previous preterm birth, cervical 'incompetence,' smoking, and nonmedical drug use. Up to now, the physiologic mechanism that initiates preterm labor is unknown. Clinical and experimental evidence has identified an association among intrauterine inflammation and preterm delivery (4). Therefore prediction and prevention of preterm delivery is very serious for improvement in neonatal outcome. Placental ischaemia and acute inflammation are the most popular pathologies that have been indicated (5). C-reactive protein (CRP) is a sensitive inflammatory marker that remains stable in maternal serum (6).

Up to now, several clinical and biochemical markers have been reported to be associated with PTD. Among those, incresed levels of maternal serum CRP are significantly associated with increased risk of PTD (7, 8). Also, measurement of cervical length (CL) and detection of cervical length have been helpful for predicting of PTD. A short CL is associated with an increased risk of PTD. Recent years, sonographic examination of the cervix has proved to be a reproducible and reliable method for the evaluation of the cervix (9).

Our aim in this study was to determine the clinical advantage of amniotic fluid CRP and maternal serum CRP obtained during genetic amniocentesis and cervical length in the prediction of preterm delivery.

Materials and methods

This prospective study was conducted in 2009 during a period of two months, involved 86 singleton pregnancies that underwent genetic amniocentesis between the 15th and 23th weeks. Research ethics approval was obtained before the initiation of the study and written informed consent was obtained from all patients. Amniocentesis was performed for advanced maternal. Included criteria were (I) have a singleton pregnancy between 15 to 23 weeks of gestation, (II) a known gestational age, (III) normal pregnancy course before the procedure, (IV) absence of congenital malformations or chromosomal abnormality and V) be older than 18 years.

Patients with presence of fetal chromosomal abnormalities were excluded after amniocentesis. Gestational age was based on the last menstrual period and confirmed by sonographic examination, prior to 20 weeks of gestation. All the pregnancies were followed until delivery. Women with spontaneous preterm delivery before 37 weeks (preterm delivery group, n = 23) and those who delivered at term (term delivery group, n = 63) were compared relation to maternal characteristics, amniotic fluid CRP, maternal serum CRP concentrations and cervical length.

Procedure
Amniocentesis was performed by using a 21-gauge needle under sonographic guidance with a free-hand technique. The first 0.5 mL of amniotic fluid was obtained by using a 5-mL syringe and removed to avoid maternal contamination. Subsequently, 15–18 mL of amniotic fluid was collected by using a 20-mL syringe and used for the CRP concentration measurements. The amniotic fluid specimens were centrifuged for 10 min to obtain the cellular components for the karyotype analysis, then was processed for CRP measurements. Immediately after amniocentesis, 5 mL of venous samples were obtained for serum CRP determinations. Maternal serum CRP and amniotic fluid concentrations were determined within 1 h after amniocentesis.

Sonographic measurement of CL was done with a 5.0-MHz transvaginal probe (Medison Launches ACCUVIX V10, Mochida Siemens Medical Systems Sonovista MEU-1586, Tokyo, Japan). CL was measured by tracing the cervical canal from the internal os to the external os. We used the cut-off value of 25 mm of CL for later analysis, which is below the 10th percentile at 24 weeks of gestation in a population ultimately delivered at term (10). Then digital cervical evaluation was done with sterile gloves and lubricant to evaluate cervical dilatation and effacement.

Statistical analysis was performed with spss v.19 the multivariate analysis, were used to compare continuous variable and proportions were analyzed with fisher exact test and for quantitative variables the t- test or Mann-Whitney test were used. Receiver operating characteristic (ROC) analysis was used for determining diagnostic sensitivity and specificity of every characteristic measurement with calculating Area under the ROC curve (AUC) in our study.

Spearman rank correlation was used to assess the correlation between amniotic fluid and maternal blood CRP values and cervical length. Statistical significance was considered when probability was<0.05. (Study power was 90%)

Results

During the study period, 86 patients underwent genetic amniocentesis. Among these, one patient had

a spontaneous abortion within 2 weeks after the procedure and four patients missed the follow up. Characteristics of women with term and those with preterm delivery are shown in Table 1.

ROC analysis revealed that maternal serum CRP level had a highest AUC value (AUC=0.974) and also, was the only significant parameter in the prediction of preterm delivery among the amniotic and maternal serum CRP levels during genetic amniocentesis. Maternal serum CRP level with the cut off value of 1.2 mg/L provided the optimum combination of sensitivity 95.1% and specificity 91.8% (Fig1).

The positive predictive value for CL length with the cut off value of 25 mm was 72.1%.

Women who delivered before 37 gestational weeks had a higher maternal serum CRP level than those women who delivered >37 gestational weeks, significantly (2.85 ng/cc vs. 2.25 ng/cc; p=0.041). No statistically significant difference observed between CL and the duration of pregnancy or amniotic fluid and maternal serum CRP levels.

The amniotic fluid CRP level was not significantly higher in patient who delivered term in comparison with patients who delivered before 37 gestational weeks. (0.60 ng/cc vs. 0.50 ng/cc; P=0. 13).

Positive correlation was seen between serum & amniotic fluid CRP (r=0.313, P<0.006).

The positive association are shown between CRP and preterm delivery persisted after adjusting for pre-pregnancy body mass index and other known risk factors for preterm delivery including, race/ethnicity, and smoking.

Table 1: Patient characteristics according to the time of delivery

|	Term delivery (n=63)	Preterm delivery (n=23)	P Value
Maternal age (Years)	33.7±4.95	35.6±6.8	0.224
Gestational age at amniocentesis (weeks)	17.2±1.66	18.11±2.09	0.061
Parity	1.34±0.9	1.51±1.25	0.560
Gravidity	2.8±1.24	2.7±1.34	0.721
Maternal serum CRP level (mg/L)	3.57±4.2	4.39±4.12	0.413
Amniotic fluid CRP level (mg/L)	1.19±1.9	1.75±5.5	0.624
Cervical length (mm)	34.7±2.91	34.75±3.81	0.956
History of premature birth			
Yes	1 (1.7%)	4 (17.4%)	0.616
No	62 (98.3%)	19 (82.6%)	
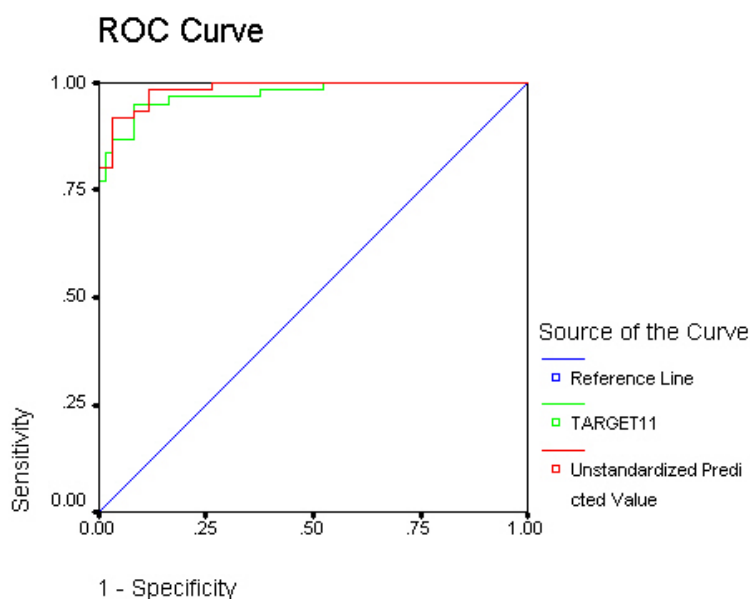
Figure 1: ROC curve for maternal serum CRP level

Discussion

Several biochemical and clinical prognostic markers have been used for preterm labor. C-reactive protein is acute-phase reactant protein that synthesized by liver cells in response to the pro-inflammatory cytokines (11, 12).

Endothelial dysfunction has been postulated is an exaggerated maternal inflammatory response to pregnancy (13).

In addition, Yudkin JS et al. indicated that CRP is strongly associated with markers of

endothelial activation and dysfunction (14). Also, these findings, showed that Creactive protein, a marker of systemic inflammation, could be involved in the pathogenesis of preterm delivery.

In the present study, we found that elevations in maternal serum CRP concentrations in early pregnancy are positively correlated with preterm delivery risk. It seems that, increased CRP levels were associated with an increased risk of delivery prior to the completion of 34 weeks gestation. Against, Ghezzi et al reported, no association between maternal blood CRP levels and risk of moderate preterm delivery (34-36 weeks) or very preterm delivery (<34 weeks) (15).

In our study, optimum cut-off value of 1.2 mg/L for the serum CRP concentration in the predicted of preterm delivery at <37 gestational weeks with sensitivity and specificity 95.1%, 91.8%, respectively.

Our study, confirms the recently published study of Ghezzi et al and supports the hypothesis that subclinical fetal inflammatory response might occur very early during pregnancy in fetuses, who will experience preterm delivery. Also, these investigators have reported the optimum cut-off value of 0.11 mg/L with a sensitivity of 80.8% and a specificity of 69.5% for the amniotic fluid CRP concentration in the prediction of spontaneous preterm delivery at <34 gestational weeks.

In the study by Ghezzi et al. showed that amniotic fluid CRP concentration of > 110 ng/mL had a sensitivity of 80.8% and a specificity of 69.5% in prediction of spontaneous preterm delivery (15). Ozer et al. did not find any difference with respect to mean CRP levels among term and preterm deliveries (16).

Our present study, demonstrated that, positive predictive value for CL length with the cut off value

of 25 mm was 72.1% in diagnosing for preterm labor. Against, in other study by Iams JD et al, reported that the positive predictive value for transvaginal cervical measurement in asymptomatic pregnant women was poor (35%) (17).

Heath and colleagues studied women who were not at increased risk of preterm birth and using transvaginal ultrasound at 23 weeks. They found that 1.7 % had a cervix length less than or equal to 15 mm (18). These women accounted for 90 % of deliveries at less than 28 weeks and 60 % of deliveries at less than or equal to 32 weeks. This suggests that the positive predictive value of a short cervix (≤ 15 mm) is much greater for extreme prematurity (≤ 28 weeks). The authors have made formula to predict the risk of spontaneous delivery at less than or equal to 32 weeks based on cervical length at 23 weeks.

In another study showed that transvaginal ultrasound screening of cervical length can predict increased risk of preterm birth, but, there is no evidence that this information can be used to improve outcomes (19).

In our study, No Correlation observed between CL and the duration of pregnancy and also between CL and amniotic fluid and maternal serum CRP concentration.

In our study revealed that CL of the patients with preterm delivery was not less than 25mm. It means that amniotic fluid CRP level and CL in these patients have not predictive value. Also, higher level of maternal serum CRP level in patients with preterm delivery was not associated with short CL.

Limitation of this study was the timing of blood collection, the underlying characteristics populations of study and no control for confounding of variables that effect in results study.

In conclusion, elevated maternal serum CRP concentrations in early pregnancy are correlated with increased risk of PTD.

Transvaginal ultrasound for cervical measurement is a safe and effective technique to predict increased risk of preterm delivery. However, routine prenatal transvaginal ultrasound for screening of cervical length is not supported by available evidence. Transvaginal ultrasound is invasive method. For instance, maternal serum CRP measurement is a safe, simple clinically useful, cost effective, non- invasive method that may assist clinicians in evaluation for high-risk patients and

determine strategies for the prevention of preterm delivery.

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